SERUM PHENYTOIN LEVELS WITH DIFFERENT BRANDS

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Summary: Four brands of phenytoin were studied in 60 newly diagnosed epileptic patients randomly and equally placed in 4 groups. Serum phenytoin levels were estimated by EMIT and spectrophotometric methods both of which gave close values with good correlation (r=0.985). Average serum levels and the incidence of remission achieved with the 4 brands varied within statistical scatter; thus these 4 brands manifested equivalent therapeutic efficacy. In 22 patients serum level was <5 \( \mu g/ml \), in 9 of whom attacks remained uncontrolled. In 38 patients serum level exceeded 5 \( \mu g/ml \) in 2 of whom attacks were uncontrolled. In 44 out of 60 patients the 2 weeks serum levels were significantly higher (P<0.001 by paired t-test) than those after 3 months. In the remaining 16 patients the serum levels at 3 months were significantly higher than at 2 weeks levels (P<0.01).

Key words: phenytoin EMIT spectrophotometry brands

INTRODUCTION

Bioavailability of phenytoin, a weak acid sparingly soluble in water, is affected by its particle size and excipients (14) which influence its dissolution and absorption. Tyrer et al. (13) reported an outbreak of phenytoin intoxication after a change in excipient. Lund (7) showed that differences in bioavailability of various phenytoin products could result in therapeutic failure or toxicity.

In the past, short term bioavailability studies in normal Indian volunteers using various brands of phenytoin have been conducted (1,2). We report here 3 months study in 60 Indian patients receiving 4 brands of phenytoin which are commonly available in the local market.

MATERIAL AND METHODS

Sixty newly diagnosed patients (male or female) were selected from the Neurology out-patient Department of All India Institute of Medical Sciences. New Delhi. Mean
age was 30.3±11.3 years and mean weight was 55.4±5.1 kg for males and 49±7.5 kg for females. Phenytoin was given once a day before bed time; throughout this study patients weighing less than 55 kg received 200 mg per day and others received 300 mg.

The following 4 brands of phenytoin were used: Epsolin tablets of Cadila Laboratories; Eptoin tablets of Boots India; Dilantin capsules of Parke Davis, India; Epileptin capsules of Indian Drugs and Pharmaceuticals. Each tablet/capsule contained 100 mg of phenytoin. The patients were randomly placed into 4 groups of 15 each. Measures were taken to ensure that each patient was taking the assigned brand and dose (by tablet count). Side effects and toxicity of phenytoin were recorded. The period of study was 3 months.

Blood was drawn once between 14.30 and 17.00 hours at 2 and 12 weeks after initiating drug therapy. Serum was separated and stored at −20°C until analyzed. Total serum phenytoin was estimated spectrophotometrically (5) and by enzyme multiplied immunoassay technique (11) using the kits of Syva International, Palo Alto, California, U.S.A. Ultrafilterable phenytoin i.e. free phenytoin in these patients was not estimated. Also total serum proteins in these patients were not estimated.

RESULTS

Of the 120 samples of serum each obtained at 2 weeks and 12 weeks from 60 patients, all were analyzed spectrophotometrically but only 92 by EMIT. The two methods give comparable results with a strong correlation co-efficient of 0.985 (Fig. 1). The mean serum levels obtained in groups of 15 patients at 2 weeks and at 12 weeks using the brands are shown in Table I. At both times there was a considerable interindividual variation observed in the drug levels, and the mean levels attained on identical days were nearly identical and statistically not significantly different from each other. The serum levels of the drug 12 weeks were generally lower compared to the levels obtained at two weeks (Table I). However, the decline was very marginal and statistically non-significant in the case of Epsolin.

During the first two weeks after institution of phenytoin therapy none of the patients had any seizures. Subsequently i.e. between 3rd and 12th week, 11 patients had uncontrolled fits despite phenytoin coverage. The distribution of patients with uncontrolled fits in different brands and their serum phenytoin levels is shown in Table II. The serum levels of phenytoin at the two time intervals in controlled and uncontrolled patients are shown in Fig. 2.
Fig. 1: 0.05 ml and 1 ml sera of patients were processed by EMIT and spectrophotometric methods. The values obtained by the two methods gave strong correlation (r=0.985).

TABLE I: Serum phenytoin levels obtained with different brands.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Dose mean ± S.D. (Range)</th>
<th>Two weeks' serum level µg/ml (Range)</th>
<th>12 weeks' serum level µg/ml (Range)</th>
<th>P value (difference between 1st and 2nd mean values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epileptin</td>
<td>4.8 ± 0.7 (3.6 - 5.9)</td>
<td>12.6 ± 7.7 (4.9 - 31.26)</td>
<td>8.77 ± 6.7 (1.2 - 29.4)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Eptoin</td>
<td>4.7 ± 0.4 (3.9 - 5.4)</td>
<td>11.73 ± 8.4 (2.9 - 31.5)</td>
<td>8.3 ± 6.6 (1.9 - 24.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Epsolin</td>
<td>5.1 ± 0.7 (3.7 - 6.4)</td>
<td>10.49 ± 8.7 (0.46 - 32.8)</td>
<td>9.27 ± 7.7 (3.1 - 27.9)</td>
<td>NS*</td>
</tr>
<tr>
<td>Dilantin</td>
<td>4.6 ± 0.9 (3.7 - 6.4)</td>
<td>9.56 ± 8.0 (2.6 - 32.6)</td>
<td>5.45 ± 3.12 (2.06 - 10.2)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

*NS = Not significant
Out of 60 patients, 22 patients showed serum levels < 5 μg/ml at 12 weeks. In 9 of these patients fits could not be controlled (Table II). Serum level in the remaining 38 patients was > 5 μg/ml and only 2 of them had fits. The difference in the incidence of fits in these 2 groups is found significant (P<0.001).

Table II: Number of uncontrolled patients and their serum phenytoin levels in different brands.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Patient</th>
<th>Dose mg/kg</th>
<th>2 weeks' serum level μg/ml</th>
<th>12 weeks' serum level μg/ml</th>
<th>Number of fits</th>
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<tr>
<td>Epileptin</td>
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<td>5.9</td>
<td>11.6</td>
<td>1.2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3.7</td>
<td>4.9</td>
<td>2.9</td>
<td>2</td>
</tr>
<tr>
<td>Eptoin</td>
<td>1</td>
<td>4.6</td>
<td>7.1</td>
<td>2.5</td>
<td>10</td>
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<tr>
<td></td>
<td>2</td>
<td>4.2</td>
<td>2.9</td>
<td>1.9</td>
<td>35</td>
</tr>
<tr>
<td>Epsolin</td>
<td>1</td>
<td>6.0</td>
<td>0.45</td>
<td>0</td>
<td>2</td>
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<td></td>
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<td>4.8</td>
<td>15.6</td>
<td>8.6</td>
<td>20</td>
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<tr>
<td>Dilantin</td>
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<td>3.7</td>
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</table>

Fig. 2: Serum phenytoin levels at 2 and 12 weeks in uncontrolled (A) and controlled (B) patients.
DISCUSSION

Although the composition of the excipients of the 4 brands used in this study is not known to us, random analysis of tablets/capsules from each brand showed that the drug content in these tablets/capsules was according to the declared specifications. The four brands gave fairly identical mean levels of phenytoin at the two times intervals tested, and the inter-individual variability (i.e. scatter) was also similar. The reasons for the non-significant decline in the levels at 12 weeks in the case of Epsolin are not known. In addition to yielding nearly equivalent blood levels, the 4 brands appear to have equivalent therapeutic effectiveness since the proportion of uncontrolled patients in each group did not differ significantly (P>0.05).

The closeness of values for phenytoin levels obtained by EMIT and spectrophotometric methods is in agreement with our earlier observations (6). The incidence of uncontrolled fits after phenytoin therapy is reported to be around 25% (4). In the present work it was 18.3%.

In 44 out of 60 patients the 2 weeks serum levels were significantly higher than those after 3 months (P<0.001). This could be a reflection of the induction of hepatic microsomal hydroxylating enzymes which speed up metabolic degradation of phenytoin (10). The serum levels at 3 months were significantly higher in 4 and about the same in the remaining 12 patients.

Although, traditionally a level of 10-20 μg/ml of phenytoin has been considered desirable serum level and above 20 μg/ml as toxic levels, some studies indicate that in many patients adequate control is achieved at 5 μg/ml levels or even less and that in many patients levels about 20 μg/ml do not manifest toxicity (3,8,9,12). In our study, 22 patients had levels of less than 5 μg/ml and 12 of these achieved seizure control. Further 5 out of 60 patients had serum levels between 20-38 μg/ml, but they did not develop any signs or symptoms of toxicity.

Nine out of 11 uncontrolled patients had serum phenytoin levels of 5 μg/ml or less values. This finding allows a useful suggestion, namely, lack of control of epilepsy can be taken as a good clinical indication of low serum levels of phenytoin and of a cautious need to raise the dose preferably after monitoring serum phenytoin levels.

It is concluded that (a) EMIT and spectrophotometric methods give comparable serum phenytoin levels and (b) that the four brands tested result in nearly identical serum levels within statistical scatter and showed equivalent therapeutic efficacy.
ACKNOWLEDGEMENTS

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REFERENCES


